SHORT COMMUNICATION

In-silico Molecular Interaction Studies of Biologically Active Secondary Metabolites of *Cissus quadrangularis* L. as a Potential Anti-cancer Drug

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DOI: 10.18811/ijpen.v9i02.10

Abstract

Cissus quadrangularis Linn. is a succulent perennial plant of family Vitaceae also called as Asthisandhaanak or Hadjor in Hindi, has been traditionally described in Ayurveda and Siddha literature as general tonic and as a powerful analgesic, used as an anti-cancer, anti-diabetic, antibacterial, hepatoprotective and neuroprotective etc. It is a good source of biologically active secondary metabolites with various pharmacological activities implicated in a wide range of human diseases. Cancer is a major issue or concern in public health systems, especially in developing countries like India. Matrix metalloproteinases (MMP), Tyrosine kinase (TK) and Vascular endothelial growth factor (VEGF) are emerging as an important cancer target therapeutic proteins. Molecular docking studies provide a better insight into the biological activity of secondary metabolites like Resveratrol (3,4′,5-*trans*-trihydroxystilbene) and Piceatannol (3,3′,4,5′-*trans*-trihydroxystilbene) from *C. quadrangularis* L., its possible mechanisms of action, binding modes and predicting it as a possible anti-cancer drug with and lesser or no side effects.

Keywords: MMP, Resveratrol, Piceatannol, Tyrosine kinase, *Cissus quadrangularis*

International Journal of Plant and Environment (2023) **ISSN:** 2454-1117 (Print), 2455-202X (Online)

Introduction

Cissus quadrangularis L., a member of Vitaceae, often known as "Hadjod" is comprehensively utilized as herbal remedy in India. Studies have reported that *C. quadrangularis L*. extract possesses anticancer, anti-hemorrhoidal, anti-microbial, anti-inflammatory and analgesic activities etc. (Mishra *et al*., 2020). The extract of *C. quadrangularis L*. contains triterpenes, flavonoids and stilbenes (Adensaya *et al*., 1999). Several bioactive stilbenes were isolated from *C. quadrangularis L*. and they have proved pharmacological activities (Sathish *et al*., 2012). Resveratrol (3,4′,5-*trans*-trihydroxystilbene) and Piceatannol (3,3′,4,5′-*trans*-trihydroxystilbene) are two naturally occurring stilbene of *C. quadrangularis L*., presents an ample scope for biochemical activities and shows promising effects as antitumour, antioxidative, anti-inflammatory, anti-microbic etc (Chopra,1986; Unnati,2011).

One of the most investigated bioactive compounds of *C. quadrangularis L*. is Resveratrol. Studies have shown that resveratrol is effective against some of the diseases. Most of the studies have the opinion that Resveratrol, a nutritious polyphenol, confer sound health & defend against miscellaneous health and age-related issues. (Chauhan and Tanuja, 2021). Moreover , Piceatannol , a hydroxylated resveratrol is less studied than resveratrol but possesses several bioactivities and health advantages like anti-inflammatory, immunomodulatory effects, used in cancer, liver diseases, diabetes, obesity, Alzheimer's sickness, and Parkinson's sickness.

One of the major burdens all over the world is cancer. A report of 2002 revels that 6.7 billion people lost their life due to cancer and 24.6 million are fighting for survival with it on this globe (Dai *et al.,*2010). Every year 12.7 million new cancer patients are reported by International Association of Cancer Registries (IACR – GLOBOCAN database) followed by 7.6 million deaths due to cancer every year (Ferlay *et al*.,2010). The latest information from database of 2018 had reported 9.6 million cancer deaths with increasing new cases to 18.1 million, which proves the effect of socio -economic devastation caused by cancer to the mankind. (Bray *et al.,* 2018). Therefore, the need of hour is to develop new therapeutic strategies on urgent basis with no or fewer side effects, to combat malignant conditions.

Testing evaluation and exploration is an influential tool for discovering bioactive with distinct structure and action mechanism. 114000 extracts from various medicinal plants have been screened by the National Cancer Institute which possess anti- cancer activities (Shoeb *et al*., 2005). Increasing health concern forced us to look forward for a cure from natural sources or a synthetic product based on natural model (Cragg *et al*., 1997). Since last few decades, plant-based products turned out to be as an extensively suggested remediation to the clinical management of cancer (Shoeb,2006). Various studies have been done to explore the anticancer activity of phytochemicals as they are copious with antioxidants, and are well known to combat cancer which in turn increases the longevity of life (Nagendra *et al*., 2010).

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How to cite this article: Chauhan, A., Kumar, A. and Tanuja. (2023). *In-silico* Molecular Interaction Studies of Biologically Active Secondary Metabolites of *Cissus quadrangularis* L. as a Potential Anti-cancer Drug. International Journal of Plant and Environment. 9(2), 168-171.

Submitted: 03/04/2023 **Accepted:** 21/05/2023 **Published:** 21/08/2023

The physiological process of cell death is defined by apoptosis which have no induced responses due to inflammation and its well-regulated mechanism makes it a better and safe a therapeutic target (Chakravarti *et al*., 2012). Various techniques are in use to induce apoptosis such as adoptive cell therapies, chemotherapy, anti-cancer antibodies, radiation, etc. (Simeone *et al*., 2012; Ramos *et al*., 2016) Cause of apoptosis and prevention of metastasis by tyrosine kinase (TK) activity followed by inhibition of angiogenesis and tumour vascularization (Hegedűs *et al*., 2018; Franklyn *et al.,* 2019).

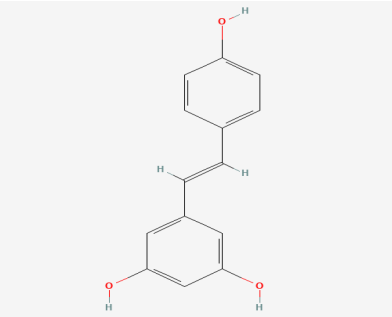
Previous studies showed apoptosis induction in carcinoma A431 and oral carcinoma KB cells by the extract of *C. quadrangularis* (Bhujade *et al*., 2013; Sheikh *et al*., 2015). Many of the active biomolecule from *C. quadrangularis L*. have demonstrated significant therapeutic potential against various cancers (Chahar, *et al*., 2011; Greenwell *et al*., 2015). So, *C. quadrangularis L*. based active molecule which may induce apoptosis is taken as therapeutic molecule against the therapeutic targets such as vascular endothelial growth factor (VEGF), tyrosine kinase (TK) and matrix metalloproteinases (MMP). Moreover, this report focuses on role of molecular interaction of resveratrol and piceatannol in combatting cancer with the aim to develop resveratrol and piceatannol into functional dietary supplements and drug.

Rule of five given by Lipinski provides a better insight to understand and predict the drug likeness of the phytochemicals or in other words we can say that it shows the similarity of phytochemicals to conventional drugs. The drug-likeness scores for *C. quadrangularis*. active phytochemicals were studied using Lipinski's principal with molecular docking against some important cancer therapeutic target proteins.

Materials And Methods

Bio actives from *C. quadrangularis* L. selected for the study was:

- **Resveratrol** (PubChem CID445154) (C14H12O3)



- **Piceatannol** (PubChem CID667639) (C14H12O4)

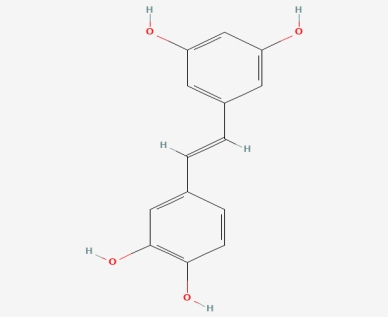


Table 1: Bio actives from *C. quadrangularis* L. with their Lipinski's properties

Serial no.	*Compounds*	*Molecular weight (Less than 500 Da)*	*Number of H bond donor (Less than 5)*	*Number of H bond acceptor (Less than 10)*	*Log P (Less than 5)*
1	Resveratrol	228.234	3	3	3.1
2	Piceatannol	244.24	4	4	2.9

PubChem (www.ncbi.nlm. nih.gov/pubchem) database which is a public database, was the platform from where the physiochemical properties and the structures of the above phytocompounds were downloaded in pdb format in accordance with the Lipinski's properties (number of hydrogen bond donors and acceptors, molecular weight and X Log P) for *C. quadrangularis*-bioactive compounds (Lipinski *et al.,* 2001).

The 3 D structure of the proteins were downloaded from the Protein Data Bank database. The RCSB PDB (www.rcsb.pdb) serves as a repository, which provides an option for advance search, and simple annotations related to 3D structural data, functions and sequence for large biological molecules. By using AutoDock 4.2 (Release 4.2.6) non polar hydrogen bonds were merged, polar hydrogen bond were added, H_2O molecules were drawn out, Gasteiger charges were calculated and the structure was cleared for the proteins.

Proteins

Tyrosine kinase (TK)PDB ID: 1M14
Domain from Epidermal Growth Factor Receptor,
Resolution: 2.60 Å
Prank Web: web server (http://prankweb.cz/)
Pocket rank: 1, Pocket score: 16.67, Probability score: 0.784
AA, count: 25, Conservation: 2.284,
X: 26.523, Y: 5.601, Z: 53.465

Vascular endothelial growth factor (VEGF) PDB ID: 1FLT,
The Flt-1 Receptor's Domain 2 in complex with, VEGF
Resolution: 1.70 Å
X: 0.38, Y: -2.98 AND Z: 20.51.

Matrix metalloproteinases (MMP)
PDB ID: MMP 1 (1HFC)
Mature Truncated Human Fibroblast Collagenase,
Resolution: 1.50 Å
X:25.232, Y: 22.367, Z: 24.321

Docking simulations results

One of the important in silico technique is Molecular docking. This technique prognosticates the modus operandi between a ligand and targeted protein for a confirmed binding site. The chemistry, affinity or strength of the compound is shown by its binding energies between a ligand and targeted protein. The lower binding energy reflects the docking compound as a possible drug candidate (Mirza *et al*.,2015; Nisha *et al*., 2016). The two naturally occurring stilbene of *C. quadrangularis L*. exhibited a good binding interaction with the binding pocket of Tyrosine kinase (TK), Vascular endothelial growth factor (VEGF), and Matrix metalloproteinases (MMP) protein (The binding affinity of the resveratrol and piceatannol as simulated by AutoDock 4.2 (Release 4.2.6) ranges from –5.8 to –5.77 kcal/mol, –6.11 to –6.54 kcal/mol, and –7.09 to –7.49 kcal/mol for VEGF, TK and MMP respectively.

Table: 2 Binding energy (Kcal/mol) of the docked compounds with Vascular endothelial growth factor (VEGF), Tyrosine kinase (TK)and Matrix metalloproteinases (MMP) protein

Compounds	*Vascular endothelial growth factor (VEGF)*		*Tyrosine Kinase (TK)*		*Matrix metalloproteinases (MMP)*	
	Binding energy (kcal/mol)	*Inhibition Constant (μM)*	*Binding energy (kcal/mol)*	*Inhibition constant (μM)*	*Binding energy (kcal/mol)*	*Inhibition constant (μM)*
Resveratrol	-5.8	55.96	-6.54	15.96	-7.09	6.35
Piceatannol	-5.77	59.28	-6.11	33.08	-7.49	3.2

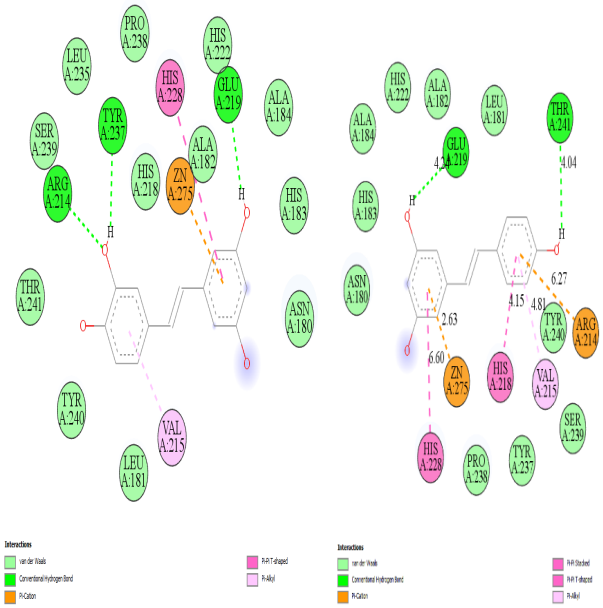


Fig. 1: Interaction of Matrix metalloproteinases (MMP) protein with Piceatannol and Resveratrol

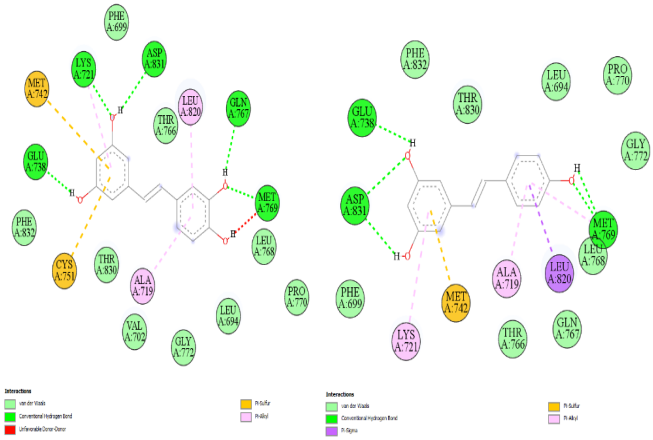


Fig. 2: Interaction of Tyrosine kinase (TK) with Piceatannol and Resveratrol

Bio actives from *C. quadrangularis L.* i.e., Piceatannol and Resveratrol showed a strong binding affinity of -7.49 kcal/mol & -7.09 kcal/mol respectively over a well-known inhibitor drug of Matrix metalloproteinases (MMP) protein, Batimastat (Franklyn *et al.*, 2019), which has binding affinity of –6.7 kcal/mol. Piceatannol and Resveratrol's binding affinity with Vascular endothelial growth factors (VEGF) was – 5.77 kcal/mol & -5.8 kcal/mol respectively, which may be opted over the known inhibitor Pazopanib (Franklyn *et al.,* 2019), which has protein binding affinity of –7.7 kcal/mol. The interaction of Tyrosine kinase (TK) with Piceatannol and Resveratrol having binding energies of -6.11 kcal/mol & -6.54 kcal/mol is comparable with the known inhibitor Imatnib (Franklyn *et al.,* 2019) with binding energy of -10.3kcal/mo. The nontoxic nature of *C. quadrangularis* makes it an appropriate, attractive alternative for the synthetic chemotherapeutic drugs.

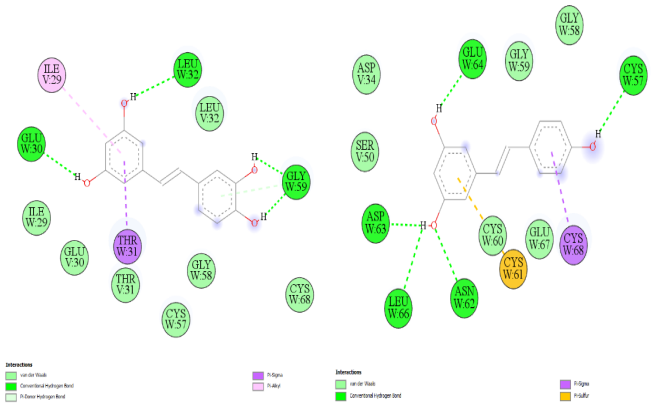


Fig. 3: Interaction of Vascular endothelial growth factors (VEGF) with Piceatannol and Resveratrol

Conclusions

The drug-likeness, non-mutagenic nature, less toxic, bioavailability and the bioactive nature of *C. quadrangularis's,* stilbenoids, showed a promising therapeutic potential as an anti-cancer drug during *in-silico* studies. The comparison of docking results of the bio actives of *C. quadrangularis L.* i.e., Piceatannol and resveratrol with well-known anti-cancer drug for vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMP) and tyrosine kinase (TK) may be considered as positive, safe and a good option for both utilization and for commercial exploitation as an anti-cancer drug. *In-silico,* in-vitro and in-vivo studies further need experimental validation for physiological pertinence of the above results.

Acknowledgement

This research work is not funded by any funding agencies. We are especially thankful to Principal, T.P.S. College, Patliputra University Patna, for providing infrastructural facilities.

Author's Contribution

Abhinav Chauhan and Arvind Kumar performed the research work and Tanuja have written and edited the manuscript.

Conflict Of Interest

None

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